REMARKS

In the Final Office Action dated June 10, 2002, Claims 1, 5, 8, 9, 11-15, 17-21, 24-25 and 30 are pending. Claims 13-15, 17-21, and 24-25 have been withdrawn from consideration as drawn to non-elected groups. Claims 3-4, 26, 28 and 29 have been canceled previously. Claims 1, 5, 8-9, 11-12 and 30 are currently subject to examination on the merits.

Claims 1, 5, 12 and 30 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. Claims 1, 5, 12 and 30 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking adequate written description. Claims 1, 5, 8-9, 11, 12 and 30 have been rejected under 35 U.S.C. § 112, second paragraph.

This Response addresses each of the Examiner's rejections. Applicant therefore respectfully submits that the present application is in condition for allowance or at least in better condition for appeal. Favorable consideration of all pending claims is therefore respectfully requested.

In response to the restriction rejection, Applicant has canceled Claims 13-15, 17-21, and 24-25, without prejudice. Applicant reserves the right to file one or more divisional applications to pursue the non-elected subject matter. Applicant has also canceled Claim 30, without prejudice. Claims 1 and 12 have been amended.

Claims 1, 5, 12 and 30 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. Specifically, the Examiner alleges that a skilled artisan would not be able to utilize the information in Example 10 to generate hybridization variants that would encode polypeptides with characteristics of the IL-11 receptor α-chain because "the described features (in Example 10) are very general, and no correlation between any given domain and a definitive function has been described in such a way as to render it predictable which

hybridization variant would be reasonably expected to retain the features of the IL-11 R α-chain."

In response, the Examiner's attention is respectfully directed to the attached Declaration by Dr. Hilton (Hilton Declaration). In the Declaration, Dr. Hilton testifies that IL-11Rα has been cloned from various sources including from mouse and human cells. Dr. Hilton testifies that, to clone a nucleic acid molecule comprising a nucleotide sequence encoding IL-11Rα from murine cells, a series of oligonucleotides were generated encompassing the nucleotide sequence encoding the signature motif, Trp-Ser-Xaa-Trp-Ser ("WSXWS"). The oligonucleotides were used to screen a commercially available adult mouse liver cDNA library. *See* Examples 1-2 and Table 2 in the specification. As testified by Dr. Hilton, a clone, Nr_1-AZ-36, which contained a nucleotide sequence encoding an amino acid sequence having the motif characteristic of the haemopoietin receptor family, was then identified from the cDNA library. From the sequence of Nr_1-AZ-36, two new primers were designed and were used to rescreen the cDNA library. The murine IL-11Rα cDNA was thus cloned and expressed in a cell system. The binding studies of the murine IL-11Rα were conducted. *See* Examples 8-13 in the specification. *See* Hilton Declaration ¶ 3-5.

Dr. Hilton also testifies that, using the two new primers obtained above, full-length murine IL-11Rα cDNA was cloned. *See* Example 10 in the specification. The full-length cDNA sequences contained an open reading frame of 1296 bp which encoded a protein of 432 amino acids in length. The predicted primary sequence included a potential hydrophobic leader sequence (residues 1-23), extracellular domain with two potential N-linked glycosylation sites (residues 24-367), transmembrane domain (residues 368-393) and short cytoplasmic tail (residues 394-432). The extracellular domain contained residues characteristic of a classical haemopoietin domain (*See* Figures 1 and 2 in the specification), including proline residues

preceding each 100 amino acid sub-domain, four conserved cysteine residues, a series of polar and hydrophobic residues and a WSXWS motif. The overall structure and primary sequence of the new receptor (IL-11Rα) were most similar to the IL-6 receptor α-chain (24% amino acid identity), the CNTF receptor α-chain (22% amino acid identity) and the p40 subunit of IL-12 (16% amino acid identity). Therefore, Dr. Hilton testifies that the approach employed was very successful in identifying the IL-11Rα clone. *See* Hilton Declaration ¶ 6.

Dr. Hilton further testifies that the human form of IL-11Rα was then cloned, also employing hybridization of murine IL-11Rα cDNA. *See* Example 14 in the specification. Dr. Hilton testifies that the detection and cloning of variants of murine or human IL-11Rα genetic molecules is accomplished using similar techniques as discussed above and as described in the specification. For example, by employing the approach above, the inventor yielded a number of variants, possibly splice variants, designated Nr1-30.2, Nr1-30.3, Nr1-30.4 and Nr1-30.17. *See* Figure 1A and Example 12. *See* Hilton Declaration ¶ 7-8.

Accordingly, Dr. Hilton testifies that the specification, particularly Example 10, enables one skilled in the art to make and use the hybridization variants that retain the features of the IL-11 R α-chain. Specifically, Dr. Hilton declares that using cDNA or probes from murine or human IL-11Rα cDNA, homologous cDNA molecules would be detected from different cells or from the same cells from different sources. Dr. Hilton further testifies that any hybridization variants would still retain either some or all of the features of the IL-11Rα such as a hydrophobic leader sequence, extracellular domain with potential N-linked glycosylation sites, transmembrane domains and a short cytoplasmic tail. Dr. Hilton testifies that the extracellular domain would still contain residues characteristic of a classical haemopoietin domain including proline residues, conserved cysteine residues and a WSXWS motif. *See* Hilton Declaration ¶ 9. Finally, Dr.

Hilton declares that hybridization variants would be readily identifiable which would hybridize to SEQ ID NO:4 or its complementary form under high stringency hybridization conditions. *See* Hilton Declaration ¶ 10.

In view of the foregoing, taken with the Declaration of Dr. Hilton, the rejection of Claims 1, 5, 12 and 30 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement, is overcome. Withdrawal of the rejection is therefore respectfully requested.

Claims 1, 5, 12 and 30 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking adequate written description. Specifically, the Examiner alleges that a skilled artisan is not provided with a description that distinguishes which members of the genus of nucleic acids that hybridize under the claimed conditions encode for IL-11 R α-chains. The Examiner alleges that the claims are broadly drawn to many hybridizable nucleic acid variants while the specification describes a singular nucleotide sequence of SEQ ID NO:4, which encodes the instant polypeptide of SEQ ID NO:5. The Examiner also alleges that the specification discloses IL-11Rα variants that do not retain function.

In response, the Examiner's attention is respectfully directed to the attached Declaration by Dr. Hilton. As addressed above, in his Declaration, Dr. Hilton testifies that any hybridization variants would still retain either some or all of the features of the IL-11Rα such as a hydrophobic leader sequence, extracellular domain with potential N-linked glycosylation sites, transmembrane domains and a short cytoplasmic tail. Dr. Hilton further testifies that the extracellular domain would still contain residues characteristic of a classical haemopoietin domain including proline residues, conserved cysteine residues and a WSXWS motif. Dr. Hilton declares that hybridization variants would be readily identifiable which would hybridize to SEQ ID NO:4 or its complementary form under high stringency hybridization conditions. Dr. Hilton

further testifies that, in fact, detection and cloning a number of variants, possibly splice variants, designated Nr1-30.2, Nr1-30.3, Nr1-30.4 and Nr1-30.17 are described in the specification, particularly in Figure 1A and Example 12. Therefore, the specification provides a skilled artisan with adequate description that distinguishes the members of the genus of nucleic acids that hybridize under the claimed conditions encode for IL-11 R α-chains.

Accordingly, Applicant respectfully submits that the claims, as amended, are directed to nucleic acid molecules that encode an IL-11 R α-chain. Therefore, a skilled artisan would reasonably conclude that Applicant was in possession of the claimed genus at the time the application was filed.

Claims 1, 5, 8-9, 11, 12 and 30 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite by reciting (a) "a nucleotide sequence which hybridizes to SEQ ID NO:4 or its complementary form under high stringency hybridization conditions" in Claim 1; (b) "nucleic acid molecule further defined by the ability of an oligonucleotide to hybridize thereto under medium stringency conditions and wherein said oligonucleotide is selected from SEQ ID NOS:6 to 10 wherein said medium stringency conditions comprise 0.25-0.5% w/v SDS at greater than or equal to 45°C for 2-3 hours" in Claim 12; and (c) defined by the ability of an oligonucleotide to hybridize thereto under high stringency conditions and wherein said oligonucleotide is selected from SEQ ID NOS:6 to 10" in Claim 30. Specifically, the Examiner admits that nucleic acids that remain hybridized under defined hybridization and washing conditions, clearly set the metes and bounds of the complementary nucleic acids claimed. However, the Examiner contends that limitations, such as moderate or high stringency recited in the instant claims, are relative terms. The Examiner suggests that amending the instant claims by addition of specific supported hybridization conditions or removal of the hybridization language

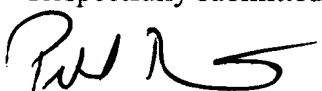
altogether.

In response, and in an effort to expedite favorable prosecution, as noted above, Applicant has amended Claims 1 and 12. Applicant has also canceled Claim 30, without prejudice. In accordance with the Examiner's recommendation, hybridization conditions have been added to Claims 1 and 12.

As such, the rejection of Claims 1, 5, 8-9, 11, 12 and 30 under 35 U.S.C. § 112, second paragraph, is overcome. Withdrawal of the rejection is therefore respectfully requested.

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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1. Declaration Pursuant to 37 C.F.R. §§ 1.132
2. Exhibit 1. Curriculum Vitae of Dr. Douglas James Hilton

PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Douglas J. Hilton	**Examiner:**	Sarada C Prasad
Serial No.:	09/532,263	**Art Unit:**	1646
Filed:	March 22, 2000	**Docket:**	10296A

For: A NOVEL HAEMOPOIETIN RECEPTOR

#13
M.J.J
4/23/03

Considered by Examiner.
4/23/03 PMJ

Assistant Commissioner for Patents
United States Patent and Trademark Office
Washington, D.C., 20231

DECLARATION PURSUANT TO 37 CFR §1.132

I, Douglas James Hilton, hereby declare as follows:-

1. I am an Applicant and co-inventor of subject matter (hereinafter referred to as the "Invention") disclosed and claimed in U.S. Patent Application No. 09/532,263 (hereinafter referred to as the "Application") which is currently under examination before the U.S. Patent and Trademark Office.

2. I hold a Bachelor of Science (BS) Degree in Biochemistry and a Doctorate Degree in Molecular Hematology. I have conducted research in the field of molecular hematology since 1986 and have authored numerous publications in this field. A true and correct copy of my Curriculum Vitae is attached hereto as **Exhibit 1**.

3. The Invention relates generally to a novel haemopoitin receptor and a method for cloning genetic sequences encoding same. More particularly, the Invention relates to the Interleukin-11 (IL-11) receptor α chain (IL-11Rα) which has been cloned from various sources including from mouse and human cells.

4. IL-11 is a functionally pleiotrophic molecule which was initially characterized by its ability to stimulate proliferation of the Inteleukin-6 (IL-6)-dependent plasmacytoma

cell line, T1165. It has since been determined to be involved in multi-potential haemopoietin progenitor cell proliferation, enhancement of megakaryocyte and platelet formation, stimulation of acute phase protein synthesis and inhibition of adipocyte lipoprotein lipase activity. It is a physiologically important molecule, therefore, and the ability to modulate its activity will have significant medical benefits in terms of therapy and the development of diagnostics. One convenient way of modulating IL-11 function is through its receptor, IL-11Rα.

5. Haemopoietin receptors generally comprise two chains, the α-chain and the β-chain. To clone a nucleic acid molecule comprising a nucleotide sequence encoding IL-11Rα from murine cells, a series of oligonucleotides were generated encompassing the nucleotide sequence encoding the signature motif, Trp-Ser-Xaa-Trp-Ser (WSXWS using single amino acid letter code), wherein Xaa (X) is any amino acid. These were used to screen a commercially available adult mouse liver cDNA library. This is described in detail in Examples 1 and 2 using oligonucleotides as described in Table 2.

A clone was identified, designated Nr_1-AZ-36 which contained a nucleotide sequence encoding an amino acid sequence having the motif characteristic of the haemopoietin receptor family. From this sequence, two more oligonucleotide primers were designed; see oligonucleotides #26 and #60, Table 2. These were used to re-screen the cDNA library. The murine IL-11Rα cDNA was thus cloned, expressed in a cell system and binding studies conducted as described in Examples 8-13.

6. For cloning of the full length murine IL-11Rα cDNA, reference should be made to Example 10. In this Example, a second murine liver cDNA library was screened using oligonucleotides #26 and #60 which are directed to the 5' end of the original Nr_1-AZ-36 clone. The key to characterizing the murine IL-11Rα cDNA was to determine its putative amino acid sequence after translation. Analyses of the cDNA sequences revealed an open reading frame of 1296 bp which encoded a protein of 432 amino acids in length. The

predicted primary sequence included a potential hydrophobic leader sequence (residues 1-23), extracellular domain with two potential N-linked glycosylation sites (residues 24-367), transmembrane domain (residues 368-393) and short cytoplasmic tail (residues 394-432). The core molecular weight of the mature receptor has been initially estimated to be approximately 36,000 daltons.

The extracellular domain contained residues characteristic of a classical haemopoietin domain (Figures 1 and 2 in the Application), including proline residues preceding each 100 amino acid sub-domain, four conserved cysteine residues, a series of polar and hydrophobic residues and a WSXWS (see paragraph 5 above) motif. The haemopoietin receptor domain of the new receptor was preceded by an 87 amino acid immunoglobulin-like domain and followed by 37 amino acids before the transmembrane domain. Regarding its overall structure and its primary sequence (see Figure 2 of the Application), the new receptor was most similar to the IL-6 receptor α-chain (24% amino acid identity), the CNTF receptor α-chain (22% amino acid identity) and the p40 subunit of IL-12 (16% amino acid identity). This approach, therefore, of considering the putative translational data was very successful in identifying the IL-11Rα clone.

7. The human form of IL-11Rα was then cloned as described in Example 14, again using hybridization of murine IL-11Rα cDNA.

8. The detection and cloning of variants of murine or human IL-11Rα genetic molecules would be accomplished using similar techniques as discussed above and as provided in the Application. In fact, the approach adopted yielded a number of variants, possibly splice variants, designated Nr1-30.2, Nr1-30.3, Nr1-30.4 and Nr1-30.17 (see Figure 1A and Example 12 in the Application).

9. My patent advisors have shown me a copy of the Official Action from the U.S. Patent and Trademark Office which *inter alia* alleges that the skilled artisan would not be

able to utilize the information in Example 10 to generate hybridization variants with the characteristics of IL-11Rα.

With respect, I totally disagree with this allegation. Using cDNA or probes from murine or human IL-11Rα cDNA, homologous cDNA molecules would be detected from different cells or from the same cells from different sources. Any hybridization variants would still retain either some or all of the features of the IL-11Rα such as a hydophobic leader sequence, extracellular domain with potential N-linked glycosylation sites, transmembrane domains and a short cytoplasmic tail.

The extracellular domain would still contain residues characteristic of a classical haemopoietin domain including proline residues, conserved cysteine residues and a WSXWS motif.

10. It is my considered opinion that hybridization variants would be readily identified which would hybridize to SEQ ID NO:4 or its complementary form under high stringency hybridization conditions. This would be readily characterized using the methods described in the Application.

11. I further declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: 3th April 2003 _____

Douglas James Hilton

Douglas James Hilton - Curriculum Vitae

1.1 Academic Qualifications

1985 BSc, Monash University.
1986 BSc Honours, University of Melbourne.
1990 PhD, University of Melbourne

1.2 Current Appointment

2000- NHMRC Principal Research Fellow

1.3 Source of Current Salary

NHMRC Principal Research Fellowship

1.4 Previous Appointments

1986-87 Research Assistant, Cancer Research Unit, WEHI.
1987-89 Tutor, Department of Veterinary Science, University of Melbourne.
1990 Postdoctoral Scientist, Cancer Research Unit, WEHI.
1991-93 Postdoctoral Scientist, The Whitehead Institute for Biomedical Research, MIT.
1993-96 Queen Elizabeth II Postdoctoral Fellow, Cancer Research Unit, WEHI.
1993-96 Project Leader, Cooperative Research Centre for Cellular Growth Factors.
1996-97 Laboratory Head, Division of Cancer and Haematology, WEHI.
1997-01 Director, Cooperative Research Centre for Cellular Growth Factors.
1998-99 NHMRC Senior Research Fellow, Division of Cancer and Haematology, WEHI.
2000-02 NHMRC Principal Research Fellow, Division of Cancer and Haematology, WEHI.

1.5 Publications

Primary Publications

1. Gearing, D.P., Gough, N.M., King, J.A., HILTON, D.J., Nicola, N.A., Simpson, R.J., Nice, E.C., Kelso, A. and Metcalf, D. Molecular cloning and expression of cDNA encoding murine myeloid leukemia inhibitory factor (LIF). *EMBO J.* 6: 3995-4002, 1987.

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Invited Reviews

1. Gough, N.M., HILTON, D.J., Gearing, D.P., Willson, T.A., King, J.A., Nicola, N.A. and Metcalf,
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Books

1. HILTON, D.J. Haemopoietic Receptors. In *Colony Stimulating Factors.* (ed. Garland, J., Hilton, D.J. and Queesenberry, P.) Marcel Dekker, New York, 1997

Book Reviews

1. HILTON, D.J. A Literary Dinosaur - Review of The Cytokine Handbook (3rd Edn). *Trends. Bioch. Sci.* 24: 461, 1999.

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3. Layton, M.J., Owczarek, C.M., Metcalf, D., Lock, P.A., Willson, T.A., Gough, N.M., HILTON, D.J., and Nicola, N.A. Complex binding of leukaemia

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1.6 Other Research Outcomes

Patents

1. **Leukaemia Inhibitory Factor**
   David Paul Gearing, Nicholas Martin Gough, DOUGLAS JAMES HILTON, Julie Ann King, Donald Metcalf, Edouard Collins Nice, Nicos Anthony Nicola, Richard John Simpson and Tracy Ann Willson.
   Australian Patent No. 609128 (granted 1991), New Zealand 224105 (granted 1991), Israel 85961 (granted 1997), Portugal 87133 (granted 1992), Japan 2682858 (granted 1997), Japan 2721123 (granted 1998), South Korea 121324 (granted 1997), Norway 178265 (granted 1996), Norway 179210 (granted 1996), USA 5187077 (granted 1993), USA 542 7925 (granted 1995), USA 544 3825 (granted 1995), Hungary 207342 (granted 1992), South Africa 88/2277 (granted 1989), Singapore 9590117.9 (granted 1994), Hong Kong 336/1995 (granted 1995), South Korea 121322 (granted 1997), USA 5750654 (granted 1998), Belgium 0285448 (granted 1994), France 0285448 (granted 1994), Italy 0285448 (granted 1994), Luxembourg 0285448 (granted 1994), United Kingdom 0285448 (granted 1994), Sweden 0285448 (granted 1994), Austria 0285448 (granted 1994), Switzerland 0285448 (granted 1994), The Netherlands 0285448 (granted 1994), Greece 0285448 (granted 1994), Spain 0285448 (granted 1994), Germany P3888379.1-08 (granted 1994)Canada 563092 (filed 31/3/88), Denmark 4831/89 (Filed 31/3/88), Finland 894613 (filed 31/3/88).

2. **Novel Receptor Ligands and Genetic Sequences Encoding Same-IIA (NLERK2)**
   DOUGLAS JAMES HILTON and Nicos Anthony Nicola.
   International Application PCT/AU96/00460 (filed 19/6/96), Australia

Application 64098/96 (filed 19/7/96), Europe Application 96923786.6 (filed 19/7/96), USA Application 08/983382 (filed 19/7/96), Japan Application 506098/97 (filed 19/7/96).

3. **A Novel Haemopoietin Receptor and Genetic Sequences Encoding Same (NR2)**
Warren Alexander, Timothy Gainsford, DOUGLAS JAMES HILTON, Donald Metcalf, Ashley Ng, Nicos Nicola and Tracy Willson.
International Application PCT/AU96/00607 (filed 26/09/96), Australia 30169/00 (granted 28/4/2000) Japan Application 513006/97 (filed 26/9/96), USA Application 09/051,843 (filed 23/10/96).

4. **A Novel Haemopoietin Receptor and Genetic Sequences Encoding Same -II (NR4)**
DOUGLAS JAMES HILTON, Donald Metcalf , Nicos Anthony Nicola, Tracy Willson, and Jian-Guo Zhang
International Application PCT/AU96/00668 (filed 23/10/96), Australia 718899 (granted 3/8/2000), Europe Application 96934193.2 (filed 23/10/96), USA Application 09/051,843 (filed 23/10/96), Japan Application 516141/97 (filed 23/10/96), Canada Application 2238080 (filed 23/10/96).

5. **A Novel Haemopoietin Receptor and Genetic Sequences Encoding Same (NR6)**
Warren Alexander, Lou Fabri, Alison Farley, DOUGLAS JAMES HILTON, Y. Kikuchi, T. Kojima, M. Maeda, Andrew Nash, Nicos Anthony Nicola, Steven Rakar, Tracy Willson and Jian-Guo Zhang.
International Application PCT/GB97/02479 (filed 11/9/97), Australia Application 43080/97 (filed 11/9/97), Europe Application 97919143.4 (filed 11/9/97), USA Application 08/928720, 09/037657 (filed 11/9/97, 10/3/98), Japan Application 513389/98 (filed 11/9/97), USA (Continuation in part) Application 09/037657 (filed 19/7/96)

6. **Therapeutic Molecules (IL-13BP)**
Nicos Anthony Nicola, DOUGLAS JAMES HILTON, Jian-Guo Zhang and Richard John Simpson
WO9810638, EP19970938678

7. **Therapeutic and Diagnostic Agents (SOCS)**
Warren Alexander, DOUGLAS JAMES HILTON, Donald Metcalf, Sandra Nicholson, Rachael Richardson, Robyn Starr, Elizabeth Viney, Tracy Willson, and Nicos Nicola.
International Application PCT/AU97/00729 (filed 31/10/97), Australia Application 46943/97 (filed 31/10/97), USA (2) Application 08/962560, 09/302769 (filed 31/10/97, 30/4/99), Norway Application 1999-2116 (filed 31/10/97), China Application 97180920.8 (filed 31/10/97), Europe Application 97909070.1 (filed 31/10/97), United Kingdom Application

9905020.5 (filed 31/10/97), Japan Application 520867/98 (filed 31/10/97), Canada Application 2270171 (filed 31/10/97), Korea Application 10-1999-7003904 (filed 31/10/97), Hong Kong Application 99105114.2 (filed 8/11/99).

8. **Novel Proteins, Their Derivatives, Homologues and Analogues and Uses Thereof (SOCS BOX)**
Warren Alexander, Manuel Baca, DOUGLAS JAMES HILTON, Donald Metcalf, Sandra Nicholson, Nicos Nicola, Tracy Willson and Jian-Guo Zhang.
International Application PCT/AU99/01134 (filed 21/12/99).

9. **A method and agents useful for same**
Manuel Baca, DOUGLAS J. HILTON, Nicos A. Nicola, Jian-Guo Zhang, Louis Fabri, Andrew Nash
PCT/AU01/00263 filed 9/3/2001

10. **Therapeutic and diagnostic molecules – II**
Sandra Nicholson, Donald Metcalf, Tracey Willson, Jian-Guo Zhang, DOUGLAS HILTON, Warren Alexander, Nicos Nicola, Francesca Walker
Australia Provisional PR5566/01 (filed 8/6/2001)

11. **Therapeutic and Diagnostic Molecules**
DOUGLAS HILTON, Nicos Nicola, Warren Alexander, Robyn Starr, Sandra Nicholson, Tracey Willson, Elizabeth Viney, Stephen Rakar, Danielle Krebs, Manuel Baca, Rachel Uren
US Provisional 60/327381 (filed 5/10/2001)

12. **In Vitro Propagation of Embryonic Stem Cells**
Nicholas Martin Gough, DOUGLAS JAMES HILTON and Robert Lindsay Williams.
PCT AU89/0030, Australia 623922 (granted 1992), USA 5166065 (granted 1992), Japan 2740320 (granted 1998), EUROPE, Germany 0380646 (granted 1999), Switzerland 0380646 (granted 1999), Austria 0380646 (granted 1999), Sweden 0380646 (granted 1999), Belgium 0380646 (granted 1999), The Netherlands 0380646 (granted 1999), Luxembourg 0380646 (granted 1999), Italy 0380646 (granted 1999), United Kingdom 0380646 (granted 1999), France 0380646 (granted 1999), Canada 607433 (filed 3/8/89), Denmark 017091 (filed 3/8/89) Norway 91/0385 (filed 3/8/89)Hong Kong 98102359.4 (filed 20/3/98)

13. **A Novel Haemopoietin Receptor (IL-11R)**
DOUGLAS JAMES HILTON.
Australia 690743 (granted 1998), International Application PCT/AU95/00578 (filed 5/09/95), EUROPE Application 95931079.8 (filed 5/09/95), Canada Application 2197873 (filed 5/09/95), Japan Application 509002/96 (filed

5/09/95), USA Application 702665 (filed 21/12/96), Hong Kong Application 98103762.3 (filed 2/5/98).

14. Novel Molecules and Uses Thereof (DAN/CER)

Christine Biben, Louis Fabri, Richard Harvey, DOUGLAS JAMES HILTON, Maria Lah, Andrew Nash and Edouard Stanley.
International Application PCT/AU98/00078 (filed 11/2/98), Australia Application (filed 58486/98), USA Application (filed 09/022115).

15. A biologically active complex

Andrew Nash, Kim Jachno, Louis Fabri, Yasuhiko Nakata, Masakazu Hasegawa, Kate Reid, DOUGLAS HILTON, Perry Bartlett
PCT/AU00/01216 filed 6/10/2000

Commercialisation/Industry Activity

LIF

1987- Human and mouse LIF are purified and cloned and patents covering LIF are lodged and assigned to AMRAD.

1988- LIF shown to inhibit ES cell differentiation, patent filed and assigned to AMRAD. AMRAD forms subsidiary, AMRAD Biopharmaceuticals, to manufacture and distribute LIF under the product name ESGRO. AMRAD Biopharmaceuticals sold to Chemicon P/L. License to LIF in inhibition of ES Cell Differentiation transferred to Chemicon.

1988-90 LIF licensed by AMRAD to Merck and Co. to investigate role in bone biology.

1990-95 LIF licensed by AMRAD to Sandoz Pharma AG to investigate LIF's potential in amelioration of thrombocytopenia.

1994-99 LIF licensed to Chugai to investigate LIF's potential in amelioration of thrombocytopenia.

1996- AMRAD begins preclinical and clinical development of LIF for amelioration of neurological impairment associated with chemotherapy. Phase I clinical trials completed successfully with the initial Phase II trial to be completed in 2002.

2000- LIF licensed to Ares-Serono for use in the area of reproductive biology; preclinical and clinical development for indications in this area begin.

IL-13Rα1

1994-00 Cloning of novel hemopoietin receptors forms major focus of research collaboration between Division of Cancer and Hematology, AMRAD and Chugai. Patents covering IL-11Rα, leptin receptor, IL-13Rα1 and NR6 are lodged.

1999- Division of Cancer and Hematology, AMRAD and Medarex execute research agreements to derive human anti-human IL13Rα1 antibodies with a view to testing their efficacy in treating asthma and allergic disease. AMRAD and Division of Cancer and Hematology collaborate to humanize a mouse anti-human IL13Rα1 monoclonal antibody.

SOCS

1997- SOCS proteins are discovered and matter of substance and utility patents are lodged.

1998 IP covering some of the SOCS molecules is licensed to AMRAD for commercial development. Research collaboration between AMRAD and members of the Division of Cancer and Haematology begins. In collaboration with AMRAD and Cerylid high throughput screens are performed to find small molecular weight SOCS inhibitors.

2000- AMRAD sublicenses a part of the SOCS IP to GSK in order to bolster drug discovery efforts. Research collaboration expands to approximately 70 scientists in GSK, AMRAD and the Division of Cancer and Hematology.

Genetics

1999- Co-Founder, Murigen Pty Ltd (with Prof. Nick Nicola, Dr Warren Alexander and Dr Simon Foote).

2000- MuriGen signs 4 year $7M contract with an International Agricultural Company..

Industry Involvement

1992-93 Consultant, Arris Pharmaceutical Company.

1993-95 Consultant, AMRAD Corporation.

1995-97 Director, Cytokine Research, AMRAD Corporation.

1995-98 Member Scientific Committee Overseeing Collaboration with Chugai Pharmaceutical Co.

1997-02 Consultant AMRAD Corporation.

1997-01 Director, CRC-CGF.

1999-00 Consultant, AMGEN through Wray and Associates (Patent Lawyers).

2001-02 Member Scientific Committee Overseeing Collaboration with AMRAD and GSK.

1.7 Other Professional, Academic or Related Activity during program period

Teaching

Organisation of Undergraduate Research Opportunity Program for the CRC-CGF (approximately 1 day per quarter).

Industry Consultation

Approximately 1 day per week, in commercialisation and application of research through links with AMRAD (SOCS and IL13Rα1), GSK (SOCS) and MuriGen (Genetics).

Administration

NHMRC New Program Grants Committee (approximately 2 days per quarter).

1.8 Research Grant Support 1997-2003

1993-98 Queen Elizabeth II Postdoctoral Fellowship and Support (~$70,000 pa).
1997-01 CRC-CGF Director's Discretionary Allocation (~$85,000 pa).
1997-99 $300,000 pa, AMRAD, Haemopoietic Growth Factors
1997-00 $700,000pa, Cooperative Research Centres Grant, CRC Cellular Growth Factors
1997-01 $1.0m pa AMRAD grants (SOCS, LIF/IL-6, NR4,NR6)
1998 Wellcome Trust Equipment Grant for FACS with Shortman, Strasser, Tarlinton and Battye ($245,178).

b) Currently Held Grants

2001-05 $340,000 pa, NIH ROI-CA-22556, Differentiation of Granulocytes and Macrophages
2001-04 $920,000 pa, Share of Cooperative Research Centres Grant, CRC for Cellular Growth Factors
1997-04 $1.0 m pa AMRAD/GSK grants (NR4, NR6, SOCS, LIF/IL-6)
2003-07 $400,000 of a $2.75 m pa, NH&MRC Program Grant (Molecular regulation of blood cell formation).

c) Grants Requested/to be Requested for 2003

None

1.10 Other Relevant Achievements

a) Honours and Awards

1984 Australian National University Vacation Scholarship.
1986 Macfarlane Burnet Prize, Ormond College, University of Melbourne.
1987-90 Anti-Cancer Council of Victoria, Postgraduate Scholarship.
1989 SEC Science and Technology Award.
1989 Victorian Young Achiever of the Year.
1991-93 Lucille P. Markey Visiting Fellowship.
1993-96 Queen Elizabeth II Postdoctoral Fellowship.
1994&96 Anti -Cancer Council of Victoria, Hillcrest Friendship Club Research Award.
1996 Anti -Cancer Council of Victoria, Graham Middleton Research Award.
1997 The Burnet Prize, The Walter and Eliza Hall Institute of Medical Research.
1998 Gottshcalk Medal, Australian Academy of Science.
1999 Australian Institute of Political Studies, Victorian "Tall Poppy".
2000 Amgen Medical Researcher Award, ASMR.
2001 Inaugural Commonwealth Health Minister's Award for Excellence in Health and Medical Research

b) Postgraduate and Undergraduate Teaching

Undergraduate Supervision

1998- Piloted Undergraduate Research Opportunity Program (UROP) through in The Division of Cancer and Hematology at WEHI. This program provides 2nd and 3rd year undergraduate students with an opportunity to carry out research over a longer time period than a typical vacation scholars program (i.e. 6 months to 2 years versus 6 to 8 weeks). This Program was piloted in 1998 with a single student and expanded through funding and administrative help through the CRC-Cellular Growth factors, The CRC-Discovery of Genes for Common Human Diseases, The Biotechnology Industry and a DETYA grant administered through the University of Melbourne. The program has approximately 30 students at anyone time and, over the last three years, students from 5 different tertiary institutions in three states have been placed in CRC and non-CRC laboratories and in academic and industry laboratories.

1994 R. Clark, BSc Hons.
1995 A. Ng, BMedSci.
1996 R. Richardson, BSc Hons.
1998 M. Brysha BSc Hons (with Robyn Starr).
1998-99 A. Herlihy BSc (UROP, with B. Kile).
1999 S. Gras BSc/BEng (UROP, with J-G. Zhang).
1999-00 M. Carpinelli BSc (UROP) and BSc Hons (with S. Foote and I. Wicks).
1999-00 B. Fishley BSc (UROP, with B. Kile).
1999-00 E. Fridel BSc (UROP, with S. Nicholson).
2000-03 K. Greig B Sc (UROP).
2002-03 L. Mielke (UROP).

Postgraduate Supervision

1997-01 R. Richardson, PhD.
1998-01 B. Kile, PhD (with Warren Alexander).
1999-02 A. Cornish, PhD (with Warren Alexander).
1999-02 D. Krebs, PhD (with Warren Alexander).
2002- S. Wormald, PhD (with T. Speed).
2003- M. Carpinelli, PhD (with
2003- M. De Brincat, PhD

Postdoctoral Supervision

1995-01 R. Starr.
1997- S. Nicholson (with N. Nicola).
1999- C. Greenhalgh (with W. Alexander).
2002- J. Antonchuk
2002- D. Krebs

Staff Scientists Supervision

1993- T. Willson.
1995- J-G. Zhang (with N Nicola).
1999- H. Martin.

Undergraduate and Postgraduate Teaching Seminars

1997 WEHI Postgraduate Lecture Series (1 Lecture).
2000 WEHI Postgraduate Lecture Series (1 Lecture).
2000 RMIT 3rd Year Molecular Biology and Immunology (1 Lecture).
2000 The University of Melbourne, Dept. Pathology 2nd/3rd Year Lecture Series 531-201/531-303 (1 Lecture).
2000 The University of Melbourne, 2nd Year Biotechnology in Practice 600-205 (1 Lecture).

c) Local, National and International Profile

Oral Presentations 1997-2001

1997 Lorne Cancer Conference, Lorne, Vic. (Invited Speaker).
1997 International Cytokine Society Meeting, Lake Tahoe, Nevada, USA (Invited Speaker).
1997 Chugai Research Symposium, Gotemba, Japan (Invited Speaker).
1998 Keystone Symposium on JAKs and STATS, Tamaron, Colorado, USA (Invited Speaker).
1998 Lorne Protein Conference, Lorne, Vic. (Invited Speaker).
1998 Haematology Society of Australia, Perth, WA (Invited Speaker).
1998 Australian Institute of Medical Scientists, National Scientific Meeting, Hobart, Tas. (Plenary Speaker).
1998 American Society of Hematology, Miami, USA (Invited Speaker).
1999 Endocrine Society Annual Meeting, San Diego, USA (Invited Speaker).
1999 Gordon Research Conference, New Hampshire, USA (Invited Speaker).
1999 24th European Symposium on Hormones and Cell Regulation, Mount St Odile, France (Invited Speaker).
2000 2nd Aachen Cytokine and Signal Transduction Workshop, Aachen, Germany (Invited Speaker).
2000 Australia's Science Future, Australian Academy of Science, Canberra, ACT (Invited Speaker).
2000 GeneOz, Heron Island, QLD (Invited Speaker).
2000 Gordon Research Conference, New Hampshire, USA (Invited Speaker).
2000 International Society of Experimental Hematology, Florida, USA (Plenary Speaker).
2000 1st Western Australian Institute of Medical Research Symposium, Busselton, WA (Invited Speaker).
2001 Keystone Symposium on Hematopoiesis, Whistler, British Columbia, Canada (Invited Speaker).
2001 Gordon Research Conference, New Hampshire, USA (Invited Speaker).
2001 ComBio Canberra ACT (Session Chairman and Invited Speaker).

2002 Keystone Symposium on JAK/STAT Signalling, Snowbird, Utah, USA (Invited Speaker, Session Chairman).
2002 Gordon Research Conference, New Hampshire, USA (Invited Speaker).
2002 10th Australian Vascular Biology Society Meeting, Newcastle, NSW Iinvited Speaker).
2002 Endocrine Society of Australia Annual Meeting, Adeliade, SA (Invited Speaker)
2002 ComBio, Sydney NSW (Session Chairman).
2002 American Nephrology Society Annual Meeting, Philadelphia, Pennsylvania, USA (Invited Speaker).
2002 Japanese Society for Immunology Annual Meeting, Tokyo, Japan (Invited Speaker).
2001 Australian Society for Medical Research Annual Meeting, Melbourne, Victoria (Invited Speaker).
2002 Ontario Cancer Institute (Invited Speaker)
2001 Keystone Symposium on Hematopoiesis, Whistler, British Columbia, Canada (Invited Speaker).

Scientific Collaborations

1987- Dr Andrew Nash, AMRAD Cytokine Group, (LIF, Cytokine Receptor, SOCS Proteins).
1990- Prof. J. Martin, St Vincent's Institute of Medical Research, Melbourne, (Cytokines in Bone Development).
1991- Dr Stephanie Watowich, MD Anderson Cancer Centre, Houston, USA (Cytokine Receptor and Signalling).
1995- Dr Ashley Dunn and Dr Matthias Ernst, LICR, Melbourne, (LIF/IL6 Signalling, Mouse Genetics).
1995- Dr Hitoshi Nomura, Chugai Institute of Molecular Medicine, Tsukuba, Japan, (Cytokine Receptors).
1998- Dr Nils Billestrup, Hagedorn Institute, Copenhagen, Denmark, (SOCS).
1998- Dr Paul Hertzog, Monash University, Melbourne (SOCS and IFN Signalling).
1999- Prof. Chris Goodnow, JCSMR, Canberra, (Mouse Genetics).
2000- Dr David Waxman, Boston University, Boston, USA (SOCS).

d) Peer Review Involvement

Grant Application Review

1993- NH&MRC (Project Grants, Program Grants, Fellowships).
1994- Dutch Cancer Society.
1994- ARC (Postdoctoral Fellowships, Small Grants, Large Grants, SPIRT Grants).
1997- Anti-Cancer Council of SA.
1997- Anti-Cancer Council of Queensland.
1998- Anti-Cancer Council of NSW
1998- Anti-Cancer Council of WA
1998- Arthritis Foundation of Australia.
1998- National Heart Foundation.
1999- Wellcome Trust (Fellowships, Joint Infrastructure Grants).

2000- MRC, UK (Program Grant)

Institutional Reviews

1997 CRC for Bio-pharmaceuticals, 5th year review.
1998 CSIRO Pharmaceuticals & Health Sector Forum.

NHMRC Committees

1998 NH&MRC Program Grant Interviewing Committee (PGIC).
1998 NH&MRC Regional Grant Interviewing Committee (RGIC).
1999- NH&MRC, Discipline Panel (DP6 1999, DP4 2000).
2000- NH&MRC, New Program Grant Committee

Editorial Board Membership

2000- Cytokine and Growth Factor Reviews.
2002- Journal of Biological Chemistry

Manuscript Review

In total I would review approximately 20 to 40 manuscripts per annum
1991- J. Biol. Chem.
1991- Science.
1993- EMBO J.
1993- J. Cell. Biol.
1993- J. Mol. Rep. Dev.
1994- Growth Factors.
1994- J. Cell Sci.
1995- Cell Growth Diff.
1996- Blood
1996- Mol. Cell. Biol.
2000- Nature, Nature Cell Biology.

e) Scientific Discipline Involvement

Membership of Professional Organisations

1999- Australian Society of Medical Research (ASMR).
2000- Australian Society of Biochemistry and Molecular Biology (ASBMB).
2001- American Society of Biochemistry and Molecular Biology (ASBMB).

Policy Development

2000 NH&MRC Grants Committee.
2000 Prime Minister's Science , Engineering and Innovation Council, Working Group on New Fields of Medicine
2001- NHMRC New Program Grant Committee.

Research Awareness Campaigns / Involvement in Wider Community

1997 Speaker, ASMR Medical Research Week Careers Night for Secondary Students (Melbourne).
1997 Speaker, ASMR Medical Research Week Careers Night for Tertiary Students (Melbourne).
1997 Speaker, Baker Medical Research Institute Student's retreat (Portsea).
1998 Speaker, Baker Medical Research Institute Student's retreat (Portsea).
1998 Speaker, Science Now (Melbourne).
1999 Speaker, ASMR Medical Research Week Careers Night for Tertiary Students (Melbourne).
1999 Speaker, Live in Workshop for High School Students (Ormond College, Melbourne).
2000 Speaker, Williamson Community Leadership Forum (Melbourne)
2000 Speaker, Future Leaders Forum '00 (Sydney and Melbourne).
2000 Speaker, "Genetics for Investment Analysts", BBY (Sydney and Melbourne).
2000 Speaker, ASMR Medical Research Week Careers Night for Tertiary Students (Melbourne)
1999 Speaker, One Day Lecture Series in Science, Secondary School Teachers (Melbourne).
2000 Speaker, Future Leaders Forum '00 (Melbourne).
2001 Speaker, Biotechnology for Fund Managers, Securities Institute of Australia (Melbourne).
2001 Speaker, CRC/AAR/AVCAL Seminar Series: So what is biotech anyway?, Sydney
2001 Scientist-In-Residence, 20 Lectures in 5 days to Year 5 through Year11 students, parents and teachers, St Ignatius College Riverview, NSW.
2002 Speaker, Future Leaders Forum '02 (Melbourne).

1.11 Statement of Record of Research Achi vement

Five Major Achievements prior to 1997:

(1) Purification and cloning of LIF.

As an undergraduate and PhD student, my mentor Nick Nicola and I purified mouse and human leukaemia inhibitory factor (LIF) allowing it to be cloned and produced as a recombinant protein. This research led to a series of papers and "matter of substance" patents which have formed the basis for successful commercial development of this cytokine.

Hilton, D.J, Nicola, N.A., Gough, N.M. and Metcalf, D. Resolution and purification of three distinct factors produced by Krebs Ascites cells which have differentiation-inducing activity on murine myeloid leukemic cell lines. *J. Biol. Chem.* 263: 9238-9243, 1988 **(Cited 112 times).**

Hilton, D.J., Nicola, N.A. and Metcalf, D. Purification of a murine leukemia inhibitory factor from Krebs Ascites cells. *Anal. Biochem.* 173: 359-367, 1988 **(Cited 98 times).**

Gearing DP, Gough NM, King JA, **Hilton, D.J.,** Nicola NA, Simpson RJ, Nice EC, Kelso A, Metcalf D. Molecular cloning and expression of cDNA encoding a murine myeloid leukaemia inhibitory factor (LIF). *EMBO J.* 6:3995-4002, 1987. **(Cited 336 times).**

Gough, N.M., Gearing, D.P., King, J.A., Willson, T.A., **Hilton, D.J.,** Nicola, N.A. and Metcalf, D. Molecular cloning and expression of the human homologue of the murine gene encoding myeloid leukemia inhibitory factor. *Proc. Natl. Acad. Sci. USA* 85: 2623-2627, 1988 **(Cited 157 times).**

Patent- Leukaemia Inhibitory Factor
David Paul Gearing, Nicholas Martin Gough, **Douglas James Hilton**, Julie Ann King, Donald Metcalf, Edouard Collins Nice, Nicos Antony Nicola, Richard John Simpson and Tracy Ann Willson.

(2) Characterization of LIF receptors.

Following the purification and cloning of LIF, I defined the breadth of cells capable of responding to LIF by careful analysis of the distribution and properties of cell surface LIF receptors. This work contributed to the notion that cytokine receptors have high and low affinity states and therefore may be composed of low affinity binding subunits and affinity converting subunits.

Hilton, D.J., Nicola, N.A., and Metcalf, D. Specific binding of murine leukemia inhibitory factor to normal and leukemic monocytic cells. *Proc. Natl. Acad. Sci. USA* 85: 5971-5975, 1988. **(Cited 111 times).**

Hilton, D.J., Nicola, N.A. and Metcalf, D. Distribution and characterisation of murine LIF receptors. *J. Cell. Physiol.* 146: 207-215, 1991. **(Cited 80 times).**

Hilton, D.J. and Nicola, N.A. Kinetic and equilibrium analyses of LIF binding to receptors on cells, membranes and in detergent solution. *J. Biol. Chem.* 267: 10238-10247, 1992. **(Cited 34 times).**

(3) Biological Characterization and Commercial Application of LIF.

Studies I performed in collaboration with members of this program and others led to the realisation that LIF regulates a diverse array of biological effects and providing one of the first demonstrations of cytokine pleiotropy. Among the important effects of LIF that we discovered are its capacity to inhibit ES cell differentiation and its ability to protect neurones from cell death. As a result of a proactive intellectual property management strategy we have built up a strong patent portfolio covering uses of LIF. This patent base has led LIF to be sold to internationally for laboratory use and through licensing to AMRAD, human LIF (emfilermin) is in phase 2 clinical trial for its capacity to ameliorate chemotherapy induced peripheral neuropathy.

Williams RL, **Hilton, D.J.**, Pease S, Willson TA, Stewart CL, Gearing DP, Wagner EF, Metcalf D, Nicola NA, Gough NM. Myeloid leukaemia inhibitory factor maintains the developmental potential of embryonic stem cells. *Nature.* 336:684-687, 1988. **(Cited 510 times).**

Allen, E.H., **Hilton, D.J,** Evely, R., Brown, M.A., Gough, N.M., Ng, K.W., Metcalf, D., Nicola, N.A. and Martin T.J. Osteoblasts display receptors for and responses to leukemia inhibitory factor (LIF). *J. Cell. Physiol.* 145: 110-119, 1990. **(Cited 80 times).**

Metcalf, D., **Hilton, D.J.** and Nicola, N.A. Leukemia inhibitory factor can potentiate murine megakaryocyte production in vitro. *Blood* 77: 2150-2153, 1991. **(Cited 88 times).**

Murphy, M., Reid, K., **Hilton, D.J.**, and Bartlett, P.F. Generation of sensory neurons is stimulated by leukemia inhibitory factor. *Proc. Natl. Acad. Sci. USA* 88: 3498-3501, 1991. **(Cited 158 times).**

Hilton, D.J. LIF: Lots of interesting functions. *Trends. in Biochem. Sci.* 17: 72-76, 1992. **(Cited 135 times).**

Patent - In Vitro Propagation of Embryonic Stem Cells
Nicholas Martin Gough, **Douglas James Hilton** and Robert Lindsay Williams.

(4) Structural and Functional Analysis of Cytokine Receptors.

As a Postdoctoral Fellow at the Whitehead Institute at MIT, in collaboration with another fellow Dr Stephanie Watowich, I provided evidence for the importance of cytokine receptor dimerization in initiating signal transduction. In addition, we revealed the role that an extracellular motif (WSXWS), which defines members of the cytokine receptor family, plays in protein folding.

Watowich, S.S., Yoshimura, A., Longmore, G., **Hilton, D.J**., Yoshimura, Y. and Lodish, H.F. Homodimerization and constitutive activation of the erythropoietin receptor. Proc. Natl. Acad. Sci. USA 89: 2140-2145, 1992 **(Cited 245 times).**

Watowich, S.S., **Hilton, D.J**. and Lodish, H.F. Activation and inhibition of erythropoietin receptor function: The role of receptor dimerization. Mol. Cell. Biol. 14: 3535-3549, 1994 **(Cited 121 times).**

Hilton, D.J., Watowich, S.S., Katz, L. and Lodish, H.F. Saturation mutagenesis of the WSXWS motif of the erythropoietin receptor. *J. Biol. Chem.* 271: 4699-4708, 1996 **(Cited 32 times).**

(5) Cloning and Biological Characterization of Novel Cytokine Receptors.

On returning to Australia, I developed a method for cloning novel cytokine receptors using short degenerate oligonucleotides encoding the WSXWS motif. In collaboration with members of this program, two of these receptors were shown to encode the interleukin-11 receptor α-chain and a shared component of the interleukin-4 and interleukin-13 receptors termed. As part of this program we also cloned the leptin receptor (first identified by others) and demonstrated its capacity to initiate signaling in blood cells. Matter of substance and use patents covering these receptors were lodged and in collaboration with AMRAD we are developing IL-13 and IL-4 receptor antagonists which we aim to test pre-clinically and clinically for their ability to ameliorate allergic disease.

Hilton, D.J., Hilton, A.A., Raicevic, A., Rakar, S., Harrison-Smith, M., Gough, N.M., Begley, C.G., Metcalf, D., Nicola, N.A. and Willson, T.A. Cloning of a murine IL-11 receptor alpha chain; requirement of gp130 for high affinity binding and signal transduction. *EMBO J.* 13: 4765-75, 1994. **(Cited 182 times).**

Hilton, D.J., Zhang, J-G., Metcalf, D., Alexander, W., Nicola, N.A. and Willson, T.A. Cloning and characterization of a novel shared component of the interleukin-4 and interleukin-13 receptors. *Proc. Natl. Acad. Sci. USA* 93: 497-501, 1996. **(Cited 179 times).**

Gainsford, T., Willson, T.A., Metcalf, D., Handman, E., McFarlane, C., Ng, A., Nicola, N.A., Alexander, W.A. and **Hilton, D.J.** Leptin can induce proliferation, differentiation and functional

activation of haemopoietic cells. *Proc. Natl. Acad. Sci. USA* 93: 14564-14568, 1996. **(Cited 158 times).**

Patent - A Novel Haemopoietin Receptor (IL-11R)
Douglas James Hilton

Patent - A Novel Haemopoietin Receptor and Genetic Sequences Encoding Same -II (NR4)
Douglas James Hilton, Donald Metcalf, Nicos Antony Nicola, Tracy Willson, and Jian-Guo Zhang

Achievements from 1997-2001:

Research:

Over the last five years my research has focussed on the regulation of cytokine signal transduction. In 1997, Robyn Starr (then a post-doc in my lab) and I expression cloned a novel negative regulator of signalling, which we named Suppressor of Cytokine Signalling-1 (SOCS-1). SOCS-1 contains a central SH2 domain and a previously undescribed C-terminal motif we termed the SOCS box. By performing database searches we identified 6 other novel SOCS proteins with SH2 domains and SOCS boxes (SOCS-2-7) and three novel protein families with ankyrin repeats and a SOCS box (ASB1-18), SPRY domains and a SOCS box (SSB1-4) and WD40 repeats and SOCS box (WSB1-2). The papers describing the identification of SOCS proteins have made a very general impact on the field and have been heavily cited **(DJH 1, cited 445 times; DJH 2 cited 157 times).**

In collaboration with members of this program and with others we have demonstrated that SOCS proteins act as part of a classic negative feedback loop to regulate cytokine signalling. We have also started to define the biochemical mechanisms by which SOCS proteins act. Through this work, we have also demonstrated that the SOCS box plays an important general role in targeting proteins for ubiquitination and degradation. Again, although this research is recent, the papers describing this work have been heavily cited. **(DJH 11, cited 107 times; DJH 17, cited 94 times; DJH 18, cited 90 times)**.
In addition to unravelling the biochemical mechanisms by which SOCS protein act, I and members of this program have focussed on determining the physiological role of SOCS proteins through the generation and analysis of SOCS deficient mice. To date we have demonstrated that SOCS-1 plays an important role in regulating IFNγ signalling and that SOCS-2 regulates the GH/IGF1 axis. **(DJH 15, cited 75 times; DJH 22, cited 72 times; DJH 27, cited 34 times).**

Recognition:

In the last 5 years my research achievements have been recognised by the award on a number of national prizes including the Gottschalk Medal of The Australian Academy of Sciences (1997), The AMGEN Medical Research Award of The Australian Society of Medical Research (2000) and the inaugural Commonwealth Health Minister's Award for Excellence in Heath and Medical Research. Over the last five years I have been invited to speak at plenary sessions of many major international meetings including the International Society of Experimental Haematology Annual Conference, The Endocrine Society Annual Meeting, several Keystone Conferences and Gordon Research Conferences.

Commercial Applications:

For biomedical discoveries to have medical application requires, in many instances, engagement with the commercial world. I have always seen this interaction as a serious responsibility and core part of a medical researcher's job description. I have taken an

active role in translating research results into patents and am an inventor on 15 patent families. I have interacted with the Biopharmaceutical sector to translate my research results into the commercial and clinical sphere, leading commercial collaborations with AMRAD, Chugai and GSK. I have provided my advice and knowledge more formally to Biotechnology companies, acting as a consultant to Arris Pharmaceuticals in San Francisco and for two years holding a joint appointment as head of Cytokine Research at AMRAD, where I continue to act as a consultant and scientific advisor.
As Director of the Co-operative Research Centre for Cellular Growth factors for five years between Jan 1997 and December 2001, I have also taken a leadership role in promoting greater understanding and interaction between the research and business communities. More recently, with four colleagues, including two members of this program, I established a consulting company Quintessential Science to provide strategic scientific advice to industry. Further, with three colleagues, again two of which are members of this program, we started a biotechnology company, MuriGen, to exploit commercial applications of mouse genetics.

Clinical Applications:

LIF, the cytokine I discovered as an undergraduate and PhD student, is currently in phase 2 clinical trial for the treatment of peripheral neuropathy associated with chemotherapy. While jointly at AMRAD and WEHI between 1995 and 1997, I acted as a "champion" for this project and played a small role in design of preclinical and clinical trials.

Contributions to the Discipline:

Over the last 8 years I have acted as an assessor for many NH&MRC project and program grants, and grants from many other agencies. In the last few years I have played an increasingly active role in contributing to the peer-review process within the NH&MRC. In 1998 I was a member of a Program Grant Interview Committee and a Regional Grants Interview Committee. In 1999 and 2000 I was a member of a Discipline Panel. In 2000 I was also a member of Grants Committee, and when this Committee split in 2001, I became a member of the New Program Grants Committee. Other aspects of my contribution to the peer-review process are detailed in my curriculum vitae.

Grants:

As an NHMRC Senior Research Fellow, and more recently Principal Research Fellow, within a block funded research institution I have received a share of the block grant to WEHI. I am also an investigator on NIH grants CA22556 and HL62275 and have received grants from the CRC-CGF and from industry to support my research.